REMARKS

Upon entry of the present amendment, claims 1, 6, 8, and 13-28 will be pending, claims 3, 4, and 9-12 having been newly canceled and new claims 23-28 added. Claims 2, 5, and 7 were previously canceled. Claims 1, 6, 8 and 22-28 are presently under examination. Claims 13-21 are withdrawn from examination as drawn to an unelected invention.

Claims 1, 6, 8 and 22 have been amended. Support for amended claim 1 is found in the specification, for example, at page 4, lines 16-18; page 11, lines 26-29; page 12, lines 14-16; page 14, lines 1-2; page 15, lines 18-30; page 16, lines 2-4; in Example 2; and in claim 3 as originally filed. Support for amended claim 6 is found, for example, in the specification at page 4, lines 10-13. Support for amended claim 8 is found, for example, in the specification at page 11, lines 1-8. Support for amended claim 22 is found, for example, in the specification at page 15, lines 1-3, and in Example 2. Support for new claim 23 is found, for example, in the specification at page 10, line 35, through page 11, line 8; and at page 16, lines 25-31. Support for new claims 24-26 is found, for example, in the specification at page 12, lines 14-18, and in Example 2. Support for new claim 27 is found, for example, in the specification at page 12, lines 28-30, and in Example 2. Support for new claim 28 is found in the specification, for example, at page 4, lines 16-18; page 11, lines 1-6 and 26-29; page 12, lines 14-16; page 14, lines 1-2; page 15, lines 18-30; page 16, lines 2-4 and 17-20; in Example 2; and in claim 3 as originally filed. No new matter has been added. Entry of the above amendment and allowance of all pending claims in view of the remarks in this Response are respectfully requested.

Interview Summary

Applicant thanks the Examiner and her supervisor for granting a telephonic interview to Applicant's representatives, Janis K. Fraser and Gretchen Temeles, on June 2, 2009. A draft amendment was sent in advance of the interview. (Though the draft amendment was faxed in error to the US Patent and Trademark Office's Official Fax No. instead of the Examiner's fax number, Applicant understands that the draft amendments are in the file as merely a draft and were not officially entered as affirmative claim amendments. Thus, the amendments presented above are based on the claims pending when the Final Office Action ("Office Action") was mailed September 11, 2008.) The draft amendment and the pending rejections for obviousness

and lack of enablement were discussed during the interview. The discussion helped clarify the grounds for the rejections and point Applicant to claim language that better addresses the Examiners' concerns. Applicant is grateful for the additional guidance courteously provided by the Examiners during the interview.

Claim objections

Claims 8 and 22 have been amended to correct the informalities noted in the Office Action at page 9.

Claim rejections under 35 U.S.C. § 103: obviousness

The Office action maintained the rejection of claims 1, 6, 8 and 22 as allegedly unpatentably obvious over Ridgway *et al.* (*Protein Engineering* (1996) 9:617-621) ("Ridgway") in view of Peipp *et al.* (*Biochemical Society Transactions* (2002) 30:507-511) ("Peipp") and Shalaby *et al.* (*J. Experimental Medicine* (1992) 175:217-225) ("Shalaby"). Applicant traverses the rejection.

As noted during the June 2, 2009, interview, the presently claimed method addresses the problem of how to efficiently produce bispecific antibodies made up of two different heavy chains and two different light chains. If all four chains are simply expressed together in a single cell, they will randomly mix-and-match into up to *ten* different four-chain antibody configurations, only one of which is the correct bispecific configuration containing two different, properly matched H-L pairs (hereinafter referred to as the HA-LA pair and the HB-LB pair, respectively). The problem can be viewed as having two independent aspects. The first aspect is ensuring that each light chain pairs with the appropriate heavy chain (i.e., LA with HA and LB with HB, as opposed to LA with HB or LB with HA). The second aspect is ensuring that when two heavy chains dimerize, they heterodimerize (HA to HB) rather than homodimerize (HA to HA or HB to HB). If both aspects of the problem are solved, the result is a bispecific, four-chain antibody, one "arm" of which is a HA-LA pair and the other "arm" of which is a HB-LB pair.

Shalaby addressed both aspects of the problem, but in a way quite different from what is presently claimed. Shalaby dealt with the first aspect of the problem by expressing one set of heavy and light chains (HA and LA) in one cell and the second set of heavy and light chains (HB

and LB) in a different cell. Each heavy-light chain pair was then separately purified from the cell in which it was expressed. The purified HA-LA pair was chemically derivatized, then chemically reacted with the purified HB-LB pair to form a four-chain heterodimer containing one HA-LA arm and one HB-LB arm. Thus, Shalaby was able to produce the desired four-chain, bispecific antibody when the two "arms" are produced in two separate cells, but did not teach how to accomplish this result when all four chains are expressed within the same cell. Critical to Shalaby's method is the fact that the two different heavy-light chain pairs were expressed and paired in separate cells.

Ridgway took a very different approach than did Shalaby, focusing on just half of the problem. Ridgway described a way to increase the proportion of heterodimerization that occurs between two different heavy chains (HA and HB), rather than homodimerization between two HA's or between two HB's. He did this by the "knobs-into-holes" technique, designing a "knob" mutation on one heavy chain that fit into a "hole" mutation designed on the other heavy chain. Because one of these "heavy chains" was actually CD4-IgG, which does not pair with a light chain, he was able to employ just one light chain in his experiment (see page 617, second column, last paragraph of the introduction section). This meant that he did not need to address the other aspect of the overall problem, i.e., how to ensure that two different light chains pair up properly with their cognate heavy chains. His only suggestion that could be interpreted as a way to solve the latter aspect of the problem is his mention of diabodies in the last sentence on page 620. A diabody contains just two polypeptides, each of which has a heavy chain variable domain (not an intact heavy chain) recombinantly linked to a light chain variable domain (not an intact light chain). If the two polypeptides have different specificities, the resulting diabody is a bispecific diabody. Such a solution to the problem is distinct from the solution represented by the present claims, which require the use of four different chains: two light chains and two heavy chains.

The Peipp reference also mentions the knobs-in-holes technique for heterodimerizing two different heavy chains to produce a bispecific antibody (see page 510, first column), but, like Ridgway, does not say anything about how to solve the issue of mismatched heavy and light chains on one or both arms, when producing a four-chain bispecific antibody. On page 510, Peipp does discuss using recombinant techniques to express heavy and light chain variable

domains together in a single polypeptide chain, a strategy that, as discussed above in the context of Ridgway, would solve the issue of mismatched heavy and light chains. Indeed, Table 2 of Peipp lists eight examples of bispecific antibodies; each one is either a diabody (formed of just two recombinant polypeptide chains, each containing one heavy chain variable domain linked to one light chain variable domain) or a single-chain bispecific antibody (formed of a single recombinant polypeptide chain containing all four variable domains). Nowhere does Peipp suggest any means by which to solve the problem of obtaining properly paired heavy and light chains when expressing two different light chains and two different heavy chains in the same cell. One reading Peipp would understand that the best way to obtain proper pairing of heavy and light domains is to produce the heavy-light chain pairs as recombinant single-chain polypeptides with both a heavy and a light chain variable domain linked together. Such a solution is not within the present claims.

In sum, Applicant submits that there is no motivation in any of the cited references, taken alone or together, to carry out the presently claimed method. None of the references says anything about controlling the timing of expression of heavy and light chains within a cell for any reason. Taken together, the references teach that, in order to ensure proper pairing of heavy and light chains in a bispecific antibody context, one should either (a) express one pair in one set of cells and the other pair in a different set of cells, or (b) reconfigure them as recombinant diabodies or single-chain bispecific antibodies. Neither of these prior art solutions is even close to what Applicant is claiming. Withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph: lack of enablement

The Office action at pages 10-16 sets forth a new rejection of the claims for alleged lack of enablement. The Office action at page 10 acknowledges that the specification is enabling

> for a method of transfecting a eukaryotic cell with a vector or vectors encoding the light and heavy chain of one pair and a vector or vectors encoding the light and heavy chain of a second pair where each pair is under the control of a different regulatable promoter in order to differentially express each pair and allow for the pairwise assembly of the expressed pairs through a knobs-to holes mutation introduced into the heavy chain portion of the first and second heavy chain.

However, the Office action goes on to say that the specification "does not reasonably provide enablement for inducing just any kind of cell to express a first light chain and a first heavy chain at one time and to express a second light chain and a second heavy chain at a different time under just any conditions." As the Applicant understands it, the rejection rests on five grounds:

(1) it would allegedly require undue experimentation in order to obtain and produce bispecific antibodies in "any" kind of cell, including wildtype cells;

(2) it would allegedly require undue experimentation to employ an "endogenous promoter" in the methods of the invention;

(3) it would allegedly require undue experimentation to construct a polycistronic vector;

(4) it would allegedly require undue experimentation to regulate the expression of the various light and heavy chain pairs; and

(5) it would allegedly require undue experimentation to carry out the "knobs-into-holes" technique.

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These grounds are addressed below.

Grounds (1) – (4) Applicant believes that the present claims address the Examiner's concerns about "any cell" as expressed in the Office action and as elaborated in the June 2, 2009 interview. The claims now are limited to use of a "eukaryotic" cell (rather than "any" cell), directly addressing the first ground for rejection listed above. As explained in the interview, one wishing to practice the claimed method would not need to find a wildtype cell and somehow induce endogenous promoters in it in order to carry out the claimed method. Even before the present amendment, the claims were not limited to such an unlikely scenario. Rather than make the experiment as difficult as possible by trying to utilize hypothetical endogenous genes with hypothetical endogenous inducible promoters, one of ordinary skill in the art would presumably seek a simple route to the final result: e.g., transfecting the cell with recombinant nucleic acid encoding the four polypeptides, with expression of the mRNAs encoding the polypeptides driven by known inducible promoters. Applicant has amply taught one of ordinary skill in the art how to do that. There is no reason to expect that the particular inducible promoters selected would be critical. And there is no reason to suppose that the structure of the vector is critical.

Polycistronic vectors (i.e., with two or more coding sequences in series, all transcribed as a single transcript from a single set of transcription control sequences) are well known in the art, as are vectors in which multiple coding sequences are controlled by separate promoters so that multiple transcripts are produced from a single vector. In the methods of the invention, the four polypeptides could be encoded on two separate bicistronic vectors, as illustrated in Example 1 of the specification. Alternatively, the four polypeptides could be encoded on four separate vectors (one coding sequence per vector) or on three vectors (two coding sequences on one, and one coding sequence on each of the other two), or all on a single vector. (The vectors could, of course, be integrated into the cell's genome to produce a stably transfected cell.) The key is to ensure that expression of the first heavy chain and light chain occurs during a period of time that does not overlap the period of time during which the second heavy chain and light chain are expressed. This could be done, e.g., by use of one inducible promoter to drive expression of the first heavy and light chains in a bicistronic vector, or use of two identical such promoters arranged on one vector or on two separate vectors; and a similar arrangement (again on one or two vectors) with a different type of inducible promoter used to drive expression of the second heavy and light chains. More complicated scenarios in which three or four different types of inducible promoters are used could also be envisioned; in such a case, two different inducible promoters (one for the first heavy chain and another for the first light chain) would be induced simultaneously or sequentially, then their induction ceased, and then two more different inducible promoters induced either simultaneously or sequentially to drive expression of the second heavy and light chains, respectively. All of this would be readily done using ordinary techniques routine in the art.

Ground (5) As discussed in the interview, it is believed that the Examiner's concerns regarding the level of experimentation necessary to carry out the "knobs-into-holes" technique is misplaced. That this technique is well known in the art is illustrated by the fact that at least three publications of record (Ridgway, Peipp and the previously-cited Carter, J. Immunol. Methods 248:7-15, 2001) describe its use in production of bispecific antibodies. Knowledge of the technique thus goes back to at least 1996. Furthermore, Applicant has demonstrated its successful use in the present methods (see Example 1 in the specification). If the Examiner

continues to believe that it would take undue experimentation to make it work, she is asked to explain the basis for her concerns so that Applicant can address them more thoroughly.

In view of the above, Applicant submits that the specification enables one of ordinary skill in the art to make and use the invention without resort to undue experimentation. Withdrawal of the rejection for lack of enablement is therefore respectfully requested.

It is believed that all claims are now in condition for allowance, and such action is solicited. Please apply any charges or credits to deposit account 06-1050, referencing attorney docket no. 14875-0154US1.

Respectfully submitted,

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